Abstract: Diagnostic criteria for provoked vestibulodynia (PVD) rely on mucosal pain in the vulvar vestibule, with less emphasis on pain from pelvic floor muscles. It is unknown how psychosocial variables associated with PVD are differentially associated with mucosal versus muscle pain. Analysis of data from the National Vulvodynia Registry (n = 202) revealed several factors associated with increased mucosal pain: pain duration ($P = .043$), the McGill sensory subscore ($P = .0086$) and the Gracely pain scale ($P < .001$). Increased mucosal pain was also associated with decreased arousal ($P = .036$). On the other hand, factors significantly associated with greater muscle pain included number of comorbid pain conditions ($P = .001$), decreased intercourse frequency post PVD onset ($P = .02$) and higher scores on the McGill sensory ($P = .0001$) and affective ($P = .0002$) subscores, the Gracely pain scale ($P = .0012$), and state anxiety ($P < .001$). Sexual function was also significantly impacted by high pelvic floor muscular pain, with lower scores for arousal ($P = .046$), orgasm ($P = .0014$) and satisfaction ($P = .013$), and higher pain ($P = .01$). Significant differences in the relationship between muscle and mucosal pain for pain duration ($P = .005$), McGill affective score ($P = .001$), orgasm ($P = .049$), change in intercourse frequency ($P = .027$), and state anxiety ($P = .030$) suggest the possibility of mucosal or muscle pain predominant PVD subtypes.

Perspective: Patients with higher pelvic floor muscle pain scores than mucosal pain scores may represent different subgroups or characteristics of patients with provoked vestibulodynia. This research highlights the importance of assessment of the pelvic floor muscles in addition to the cotton swab test of the vestibule.

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Key words: Provoked vestibulodynia, vulvodynia, pelvic floor muscle, dyspareunia.

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Introduction

Provoked vestibulodynia (PVD) is defined as pain of at least 3 months’ duration localized to the vulvar vestibule and provoked by touch and/or vaginal penetration. The etiology of PVD is unknown. Its prevalence is estimated at 8.3% of adult women.33 PVD is associated with significant psychosocial distress, impaired sexual functioning, and diminished quality of life.14 Currently, no large randomized placebo-controlled trials support an effective pharmacologic treatment for this disorder.28 Few noncontrolled studies support interventions such as pelvic floor physical therapy, cognitive behavioral therapy, and, for selected patients, vestibulotomy.24 Researchers question whether the phenotypic heterogeneity of this condition contributes to difficulties with identifying effective treatments.1,10,22,23,35,40 The 2015 revised consensus terminology3 classifies vulvodynia by location (generalized vulvar pain or localized), inciting factor (provoked, spontaneous, or mixed), onset (primary—since first genital penetration—or secondary) and temporal pattern (intermittent, persistent, or delayed). These categories in themselves do not appear to represent mutually exclusive subsets.14 Several additional features associated with vulvodynia are outlined in an appendix to the consensus criteria.3 Recent investigations propose further tailoring treatment based on these associated factors—for example, psychological distress,1,10,12 hormonal deficiency,22 inflammatory markers,9,15 presence of comorbid pain conditions,9,24,35 or pelvic floor dysfunction.28,31

Diagnostic criteria and examination recommendations for PVD have traditionally focused on the vestibular mucosa. However, recent evidence suggests that pain with vestibular contact may be inadequate to characterize penetration pain in women with PVD, as it disregards pain with pelvic floor muscle activation.2,3,29,41 Up to 90% of patients with PVD have pelvic floor muscle abnormalities when examined by physical therapists,37 including lower pain threshold and tolerance, increased resting state tone, decreased ability to contract on command, and abnormal muscle morphology.17,20,21,30 Research has not determined whether these muscle abnormalities are a source or consequence of vestibular mucosal pain, or if they are caused by other centrally mediated factors. For example, anxiety and fear avoidance are psychological features associated with heightened muscle activity and pain.6,41 Lower pain thresholds in distant body regions suggest systemic alterations in pain sensitivity consistent with central sensitization18 and evidence from functional MRI brain imaging supports the role of the motor cortex underlying tonic contractions of the pelvic floor muscles.27

The objectives of the current study were to evaluate the relationship between evoked mucosal and pelvic floor muscle pain and self-reported pain and sexual function in women with PVD. We hypothesized that the severity of muscular pain, but not mucosal pain, had a greater impact on sexual function. We further sought to determine the extent to which elements of the pain history commonly employed to subtype women with PVD, such as time of onset, hormonal contraceptive use, mood, and presence of comorbid pain conditions, were predictive of mucosal or muscular pain.

Methods

Subjects

This research used data from the National Vulvodynia Registry, a prospective cohort study of 327 participants across 8 sites enrolled from 2009 to 2014. Institutional review board approval was obtained from each site and informed consent was obtained from each study participant. Research methods for the National Vulvodynia Registry have been published previously.29 Only women with provoked vestibulodynia were included, although those with PVD and vulvar pain outside of the vestibule were not excluded. Women with genitourinary atrophy of menopause, vaginal infection, or dermatoses that may have contributed to dyspareunia were excluded by history, visual internal and external vaginal examination, and saline and KOH wet mount.

Sensory Testing and Self-Report Questionnaires

Sensory testing of the vestibule was performed with cotton swab for assessment of vulvar mucosal pain sensitivity. To assess pain sensitivity of the pelvic floor muscles, single-digit pressure of approximately 2 kg (calibrated by an algometer just before the exam) was performed at the bulbocavernousus (at 5 o’clock and 7 o’clock), levator muscles (at 7 o’clock and 5 o’clock, respectively), and the perineal complex at 6 o’clock, as previously described.28 A summary score (range 0–50) for static mucosal pain was generated by adding 5 numeric rating scale (NRS) scores (0–10) from cotton swab sensitivity tests at 10 o’clock, 5 o’clock, 7 o’clock, 6 o’clock, 5 o’clock, and 2 o’clock of the vestibule. A summary score (range 0–50) for muscular pain was generated by adding the 5 NRS pain scores (0–10) from pressure applied to the bulbocavernousus, levator complex, and the perineal body. Additionally, separate subgroup analyses of bulbocavernous pain scores and of levator pain scores were performed.

Patients completed questionnaires assessing pain related to and unrelated to intercourse, mood, and sexual function. These questionnaires included the McGill pain questionnaire,26 the modified Gracely pain scale,25 the female sexual function index (FSFI),38 the state-trait anxiety inventory (STAI),39 and the Beck depression inventory (BDI).5 History of physical and sexual abuse/trauma and presence and number of comorbid pain conditions was determined by self-report based on a prespecified list of conditions: temporomandibular disorder, endometriosis, headache, interstitial cystitis, irritable bowel syndrome, fibromyalgia, chronic pelvic pain, and general chronic pain. History of anxiety was self-reported, and patients also completed the STAI to assess degree of anxiety. History of depression was based on self-report or a score of 14 or higher on the
BDI. Vulvar pain was defined by self-report as presence of vulvar pain outside the vestibule (beyond the introitus), in addition to provoked vestibular pain.

Statistical Analysis

This analysis includes only participants with PVD from the 4 geographic sites with the most complete covariate data (n = 202). Due to incomplete questionnaire responses, some variables have fewer observations (see results section and tables for further details). Statistical analysis was carried out using STATA 15.1 (Copyright 1985–2017 StataCorp LLC). Alpha was set at .05.

Predictors of NRS Pain Scores

For unadjusted analyses, the NRS pain scores were compared across categories of each specified predictor one at a time using simple linear regression models with bootstrapping. Multivariable, adjusted analyses were additionally performed to determine which of the factors were independently associated with NRS pain scores after the remaining factors were adjusted for in the models. For the multivariable analysis, we used multiple linear regression models with bootstrapping. In both the univariate and multivariable analyses above, each NRS score was the dependent variable in the analysis. There was no evidence of multicollinearity among the independent variables. Hence, the initial multivariable model included all the potential predictors that were listed in Table 2. Final models were selected using the backwards procedure for variable selection with liberal \( P < .15 \) as the retention criterion. We used liberal \( P \) value retention criteria as this was an exploratory study and we did not wish to miss any important confounders.

We assessed whether the association of each predictor variable differed between the 2 NRS scores using a multivariate regression model where both pain score were evaluated simultaneously under the same model including the factors that were found to be significant in the previous multivariable analysis by testing the difference in the corresponding regression coefficients under the model.

Correlations Between NRS Pain Scores Versus Specified Continuous Measures

Univariate, unadjusted correlations were computed between each NRS pain score versus the McGill, Gracely, and FSFI scores using the Spearman method. The change in postvulvodynia onset “frequency of intercourse” score was defined as post-onset value minus the pre-onset value after excluding women who had pain prior to first intercourse (n = 85). Univariate correlations between the NRS pain score versus the change in intercourse frequency score were computed similarly.

Multivariable Adjusted Regression Models for NRS Pain Scores Versus Subjective Quality of Life Outcomes

We evaluated the associations between the NRS pain scores versus each of the subjective quality of life outcomes including FSFI, STAI and BDI scores using linear regression analysis. The linearity assumption was confirmed using splines. The associations between the NRS pain scores versus each binary outcome measure including anxiety and depression were evaluated using logistic regression analysis. All of the above models were adjusted for the prespecified covariates of age/ menopausal status, number of comorbid pain conditions, and prevulvodynia onset frequency of intercourse.

We evaluated the relationship between the change in intercourse frequency score as a 3 level ordinal outcome (no change or decrease by 1 category; decrease by 2 to 3 categories; decrease by more than 3 categories) versus the NRS pain scores by tertiles using the ordinal logistic model before and after adjusting for the prespecified confounders of age/menopause status and number of comorbid pain conditions after confirming the proportional odds assumption. The associations of NRS pain score tertiles versus subjective quality of life measures were adjusted for comorbid pain conditions and age, since the presence of comorbid pain and age may influence the quality of life measures and were therefore considered potential confounders.

We assessed whether the associations between the NRS pain scores versus each of the examined subjective quality of life outcomes (such as FSFI or change in intercourse frequency) differed between the 2 pain measures by evaluating the corresponding difference in regression coefficients under the above multivariable models. In all of these analyses above, the NRS pain measures were used as the independent variables whereas each specified quality of life measure was used as the dependent variable in the analyses.

Missing Data

Missing values for the covariates were singly imputed using regression imputation for the purpose of the multivariable analysis for all subjective quality of life outcomes. The analyses for evaluating the relationship between NRS measures versus the subjective quality of life outcomes such as the FSFI, STAI, or BDI scores were based on patients with complete data for the above measures. The complete case analysis that we performed assumed that the missing data were at random after conditioning on the NRS pain scores.

Results

Of the 202 women included in this analysis, 91 (45%) were from AdventHealth Orlando (formerly Florida Hospital), 5 (2.5%) from University of Central Florida, 91 (45%) from UCLA, and 15 (7.5%) from Center for Vulvovaginal Disorders in Washington DC. The average age of participants was 33.5 years (95% CI 31.9–35.1 years), with median pain duration of 21 months (range 12–360 months). The mean summary NRS pain scores for mucosal and muscle pain are presented in Table 1. Summary mucosal and muscle scores were only weakly correlated (r = .33, \( P < .001 \)) (Fig 1). We found similar results when
Factors Associated With Summary NRS Pain Scores

Mucosal Pain

In unadjusted analysis, 2 factors were associated with higher mean mucosal NRS scores: pain duration (ie, months of vulvar pain) and presence of comorbid pain disorders. Women with pain duration more than 5 years had significantly higher mean mucosal NRS score than those who had pain duration less than 1 year or between 1 and 5 years (≥ 5 years versus < 1 year: mean change = −1.32, ≥ 1 year and < 5 years versus < 1 year, mean change = 4.73, \( P = .043 \) for ≥ 5 years). Presence of any comorbid pain conditions as a categorical variable was associated with significantly higher mucosal scores (mean change 3.63, \( P = .034 \)). In adjusted analysis, the only factor associated with higher mucosal score was pain duration ≥ 5 years versus < 1 year (mean change = .44, \( P = .036 \)); presence of comorbid pain conditions was no longer significant after controlling for pain duration. None of the other factors were significantly associated with mucosal pain scores in the multivariable model. (Table 2)

Muscle Pain

In unadjusted analysis, presence and number of comorbid pain conditions were associated with a significantly higher muscle pain score (mean change 5.72 for presence of comorbid pain disorder, \( P = .001 \)). In the adjusted analysis, the only significant association was with number of comorbid pain conditions, whereas the other factors were not significant once comorbid pain conditions was controlled for in the model. (Table 2)

We also analyzed whether there was a significant difference between the relationship between mucosal pain scores and the predictor variables versus muscle pain scores and the same predictor variables. The associations of pain duration with the mucosal score were significantly different from the corresponding association with the muscle score (difference in regression coefficients for pain duration: \( P = .005 \)). We found no significant differences between the association between comorbid pain conditions and mucosal score versus comorbid pain conditions and muscle score.

Correlation Between NRS Pain Scores and McGill and Gracely Pain Scores

NRS pain scores were obtained during clinical examination, while the McGill and modified Gracely pain scores...
were reported by study participants on questionnaires. Higher scores on the McGill questionnaire reflect more severe pain. Weak correlations between mucosal and muscle pain scores and McGill sensory and affective pain scores were identified. The mucosal pain NRS score positively correlated with the McGill sensory score (\( \rho = .24, p = .0086 \)) and the muscle pain NRS score positively correlated with both the McGill sensory (\( \rho = .34, p = .0001 \)) and McGill affective (\( \rho = .33, p = .0002 \)) scores. (Table 3) We formally compared the correlations between the 2 types of NRS scores by evaluating the corresponding difference in the regression coefficients under a multivariate regression model and found that the regression coefficient of the muscle score with the McGill affective score significantly differed from the corresponding regression coefficient with the mucosal score (\( P = .001 \)). On the other hand, the coefficient of the muscle score with the McGill sensory score did not significantly differ from the corresponding regression coefficient with the mucosal score.

Another measure of pain, the modified Gracely pain scale, was used to determine pain with intercourse, with higher values indicating stronger pain. The modified Gracely pain scale correlated with both mucosal and muscle NRS pain scores (\( \rho = .42, p < .001 \) and \( \rho = .33, p = .0012 \), respectively), and the correlations were not significantly different. (Table 3)
Correlation Between NRS Pain Scores and FSFI Scores

Higher mucosal NRS scores significantly correlated with a lower FSFI arousal score ($r = -0.18$, $P = .036$), indicating diminished arousal with increased mucosal pain. Higher muscle NRS scores correlated with lower arousal ($\rho = -0.17$, $P = .046$), orgasm ($\rho = -0.26$, $P = .0017$), overall satisfaction subscores ($\rho = -0.21$, $P = .013$), and higher FSFI pain score ($\rho = -0.21$, $P = .01$). Among the muscle NRS subcategories, a higher bulbocavernosus score was significantly correlated with lower arousal ($\rho = -0.18$, $P = .017$), orgasm ($\rho = -0.27$, $P = .0014$), and satisfaction score ($\rho = -0.20$, $P = .017$). The levator NRS score negatively correlated with the FSFI orgasm score ($\rho = -0.23$, $P = .0065$) and the FSFI satisfaction score ($\rho = -0.18$, $P = .028$). (Table 4)

The relationship between the NRS scores and the FSFI subscores for orgasm and arousal remained significant.
after adjusting for age and comorbid conditions. (Table 5) We found no significant interaction effects between the 2 NRS scores.

When comparing the relationship between the mucosal and muscle NRS scores and FSFI subscore, the associations of NRS pain scores differed with only respect to FSFI orgasm, where higher muscle pain was more likely to be associated with decreased orgasm ($P = .049$).

**Relationship Between NRS Pain Scores and Change in Intercourse Frequency After Diagnosis**

There was a significant correlation between the change in intercourse frequency score and the muscle pain score ($\rho = .22, P = .02$), but not with the mucosal pain score ($\rho = -.07, P = .464$). In other words, worse muscle pain is significantly associated with a greater decrease in intercourse frequency. These relationships differed between the 2 pain measures with a difference in regression coefficients: $P = .027$.

In the ordinal logistic regression analysis, we found that women with muscle scores in the higher tertiles have significantly greater decrease in intercourse frequency, without accounting for mucosal score and other factors ($OR = 3.81, P = .0313$). For instance, the percent of those reporting a greater than 4-point score difference (indicating greatest degree of decreased intercourse frequency based on the questionnaire created for the registry) increased from 24.4% in muscle tertile 1 (NRS score range 0–15) to 34.2% in muscle tertile 2 (NRS score range 16–27) to 44.7% in muscle tertile 3 (NRS score range 28–50). After adjusting for age and number of comorbid pain conditions, the relationship between higher muscle score and decreased postonset intercourse frequency was similar and remained significant ($OR = 3.01, P = .0270$). There was no significant association between mucosal score tertile and change in postonset intercourse frequency, even after adjusting for muscle score and other factors.

In addition, we found that the above associations with intercourse frequency change between the 2 scores were significantly different with difference in regression coefficients under the ordinal logistic model: $P = .045$.

**Relationship Between NRS Pain Scores, Anxiety, and Depression**

We found no significant associations between mucosal or muscle NRS pain scores and patients’ history of either anxiety or depression.

We also evaluated responses to the STAI questionnaire among 140 subjects with known scores. We assumed that data on STAI state and trait subscores was missing at random as there were no significant differences in the NRS pain scores and the covariates between persons with and without the missing STAI subscores. We found a significant relationship between muscle NRS score—but not mucosal NRS score—and the STAI state anxiety subscore (muscle: $\rho = .25, P < .001$; mucosal: $\rho = -.05, P = .517$), indicating association of muscle pain with greater anxiety. (Table 4) Adjusted analysis yielded similar results. (Table 5) This relationship differed between the 2 pain measures (difference in regression coefficients: $P = .030$). There were no significant associations between STAI trait or BDI scores versus the NRS mucosal or muscle pain scores before or after adjusting for potential confounders.

**Discussion**

This cross-sectional analysis of a multicenter sample of women with PVD suggests pelvic floor muscle and vestibular mucosal pain may represent different aspects of the sexual pain experience, and highlights the
importance of the pelvic floor muscle exam in research studies and clinical practice. The primary objective of this investigation was to determine if women with PVD who had higher vestibular mucosal pain scores were phenotypically different from those with higher pelvic floor muscle pain scores, such that degree of mucosal and muscle pain could identify distinct and clinically relevant “mucosal” and “muscle” pain phenotypes. We assessed this relationship in 2 ways. First, we were interested in the strength of the association between mucosal and muscular NRS pain scores and specific variables relating to a patient’s medical history, pain history, anxiety, depression and sexual function. We also assessed the relationship of the muscle and mucosal pain NRS with self-reported pain and change in intercourse frequency after onset of PVD. Secondly, to confirm relevant subgroup or phenotypic differences, we analyzed whether the relationship between mucosal NRS pain scores and the variables of interest were significantly different from the relationship between muscle NRS pain scores and those same variables of interest.

A number of variables were associated with higher mucosal pain scores. Specifically, a higher mucosal NRS score was associated with longer pain duration. Mucosal NRS scores also demonstrated a positive correlation with the McGill sensory and the Gracely pain scales. Among aspects of sexual functioning, a higher mucosal NRS score was associated with a decreased score in the arousal domain. On the other hand, a higher muscle NRS score significantly associated with a greater number of comorbid pain conditions. Muscle NRS scores significantly correlated with both McGill sensory and affective subscores and the Gracely pain scale. Greater muscle pain was also widely related to worsened sexual function in the domains of arousal, orgasm, satisfaction and pain. Those with higher muscle NRS scores demonstrated decreased intercourse frequency after diagnosis of PVD, whereas a similar relationship was not found with mucosal pain. Finally, a higher muscle NRS score significantly correlated with higher state anxiety. We determined there were significant differences in the relationships between mucosal pain and muscle pain for pain duration, orgasm, change in intercourse frequency, the McGill affective subscore, and state anxiety. Phenotypic differences that emerged include the association of mucosal pain with pain duration, whereas muscle pain has a stronger relationship with anxiety and sexual dysfunction, specifically decreased orgasm, intercourse frequency, affective pain. Other aspects of the history (eg, primary or secondary PVD, vulvar pain outside the vestibule, hormonal contraceptive use, history of vaginal infections, sexual abuse, self-reported pain, history of anxiety, and depression) were not differentially associated with the mucosal or muscle NRS scores.

Our findings show that pain duration may be a defining characteristic of women with PVD and high mucosal pain. The literature suggests that longer pain duration and anxiety are associated with particular features of PVD, but the contributions of pelvic floor muscle and vestibular mucosa were not previously addressed. For instance, patients with more longstanding PVD are less likely to experience spontaneous remission and are more prone to relapse. Cognitive and psychological factors and even brain structure can affect pain persistence and severity. Catastrophizing predicts pain intensity during intercourse in PVD sufferers and can mediate who will develop chronic pain after acute injury or inflammation. Anxiety, in addition to older age of onset and presence of vulvar pain outside the vestibule, was recently shown to reflect a persistent pain trajectory in healthy women with PVD. Duration of chronic pain is in general positively associated with decreased gray matter volume, though women with vulvodynia of relatively shorter durations were noted to have increased gray matter volume. The association of higher mucosal pain with longer pain duration might suggest this group of women could respond differently to various treatments than those with higher muscle pain and could be an important factor to assess in future trials.

Predictably, both mucosal and muscle pain on examination were positively correlated with self-reported pain with intercourse. Our data suggest however, that increased muscle pain has different consequences for sexual function: a higher muscle NRS score was more widely and significantly associated with more domains on the FSFI. When we directly compared the relationship between muscle and mucosal pain scores and those FSFI domains, we found that increased muscle pain was differentially associated with worse outcomes in the orgasm domain. Furthermore, participants with higher muscle pain also significantly differed from those with higher mucosal pain scores with respect to decreased frequency of intercourse after onset of PVD. These findings are consistent with and extend prior studies. Alappattu and colleagues reported that intercourse pain was associated with both pelvic muscle and mucosal pain sensitivity, in addition to widespread pain sensitivity at remote body areas. Witzeman et al noted that muscle pain on exam, but not mucosal pain, was associated with degree of pain with intercourse. Mucosal pain severity during the cotton swab test also did not correlate with degree of sexual satisfaction. They concluded that painful penetration in women with PVD is not accurately described by measures of mucosal pain alone. Further highlighting the complexity of sexual pain in PVD, Foster et al observed that pain with tampon insertion, which has been proposed to more accurately mimic pain with intercourse, did not correlate with pain on examination of the pelvic floor muscles or pain produced during cotton swab pressure on the vestibule. Moreover, neither mucosal pain during the cotton swab test or self-reported pain during intercourse correlated with sexual satisfaction.

Finally, we failed to find an association between mucosal or muscle pain on exam and depression or trait anxiety. However, muscle pain was positively correlated with state anxiety, and this relationship was significantly different from the relationship between mucosal pain and STAI state anxiety. Alappattu et al was able to identify 2 clusters as defined by both pain severity with
intercourse and psychological distress, one with high pain sensitivity and high distress and another with low sensitivity and low distress. The study combined the muscle and mucosal pain scores for the cluster analysis, which makes it difficult to separate out the effects of muscle versus mucosal pain, but generally supports the idea that high psychological distress is associated with increased pain.

Strengths of this study include a standardized assessment of mucosal and muscular pain, as providers were trained on how to perform the physical exam component of the study. This study also simultaneously captures a broad range of a participant’s experience by collecting a large number of both medical and psychological variables. One of the main limitations of this study is that, though it captures patients from several sites from across the United States, the overall number of subjects (n = 202) may have been too small to detect more subtle trends, especially given the relatively larger number of variables analyzed. We chose not to adjust for multiple testing as this was an exploratory study with many preplanned outcomes and comparisons and we were therefore more concerned about failing to find any important associations (Type 2 error) than with erroneously finding any significant associations (Type 1 error). That said, future studies are needed to confirm the results. Moreover, the analysis was limited at times by instances of missing data in which patients did not completely answer questions, reducing the number of data points even further. This study may also be limited by its generalizability, as it drew mostly from patients who identified as white and who sought care at tertiary care centers. Lastly, this study was limited by the cross-sectional observational nature of the design, which limits our ability to evaluate all potential confounders in the relationships that we studied.

**Conclusion**

By analyzing a multisite database of patients presenting for treatment of PVD, we found that several factors may help differentiate separate phenotypes of mucosal- versus muscular-predominant vestibular pain. Compared to the other, pain duration is more strongly associated with mucosal pain, whereas anxiety and decreased intercourse frequency in women with secondary PVD are more strongly associated with muscle pain. These results generally add to previously published findings in the literature demonstrating patients with higher pelvic floor muscle pain may be phenotypically different from those with more severe mucosal pain. Furthermore, this study highlights the importance of including a simple quantifiable estimate of pelvic floor muscle pain, in addition to the cotton swab test, in patient evaluations for clinical or research purposes. Further research is needed to confirm these findings in larger patient samples and to study muscular and mucosal contributions to treatment outcomes.

**References**

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